Chemistry of the Phenoxathiins and Isosterically Related Heterocycles. XVII (1). First Synthesis of a Benzoxathiinopyridazine and the Determination of Structure by ^{13}C-NMR: 1-Methoxy-3,4-diazaphenoxathiin

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Received March 30, 1981

The reaction of 5-methoxy-3,4-dichloropyridazine with the disodium salt of *o*-mercaptophenol leads to the formation of 1-methoxy-3,4-diazaphenoxathiin as the sole product of the reaction. The structure of the isolated product was confirmed by ^{13}C-nmr spectroscopy, with the development of arguments to discriminate the isolated compound from 4-methoxy-1,2-diazaphenoxathiin, the other product possible in this reaction. Mechanistic considerations in the formation of the isolated product are discussed.

J. Heterocyclic Chem., **18**, 1165 (1981).

The dihalo- and trihalopyridazines have served as versatile starting materials for the elaboration of a diverse assortment of pyridazine derived phenothiazine (6-18), phenoxazine (19-23) and thianthrene (24,25) systems. There are three isomeric benzoxathiinopyridazines which could conceivably be derived from 3,4,5-trichloropyridazine (**1**). To reduce the complexity of the problem, we sought to limit the number of isomers possible by first converting **1** to the corresponding 5-methoxy-3,4-dichloropyridazine (**2**) by a modification of the procedure of Itai and co-workers (26). Subsequent condensation of **2** with the disodium salt of *o*-mercaptophenol (**3**), prepared according to an adaptation of the procedure of Elliott and co-workers (27), could then lead to the formation of only two isomeric products. As shown in Scheme I, the initial attack of the thiophenolate anion, which is by far the stronger of the two nucleophiles (28), on the 4-position would lead, on subsequent cyclization of the intermediate phenolate sulfide (**4**), to the 1-methoxy-3,4-diazaphenoxathiin (**5**). In contrast, initial attack of the thiophenolate anion at the 3-position would lead through the intermediate sulfide (**6**) to give 4-methoxy-1,2-diazaphenoxathiin (**7**).

After reflux, the reaction mixture was quenched with water, extracted with ethyl acetate and worked up to give a crude yellow crystalline material which recrystallized to give fine yellow needles. Examination of this material by low resolution mass spectroscopy gave an intense parent ion, $M^{\cdot+}$, m/z = 232, which is consistent with either of the two possible isomeric products. While there were not a large number of fragment ions observed, an ion at m/z = 204 (16.5%, $M^+ - 28$) was observed which probably

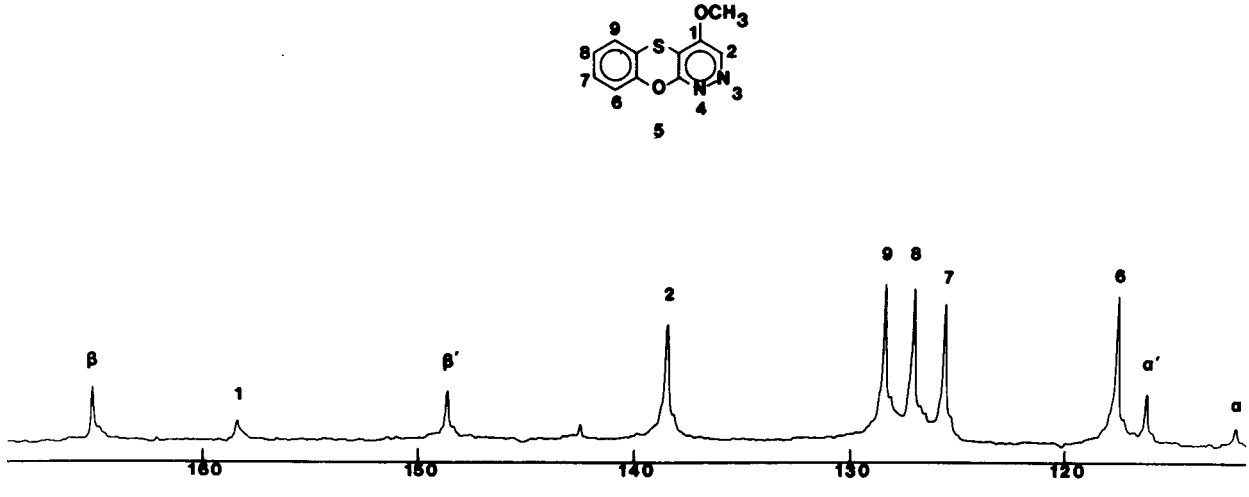


Figure 1. ^{1}H-decoupled ^{13}C-nmr spectrum of **5** in hexadeuteriodimethylsulfoxide at 25.2 MHz.

0022-152X/81/061165-04$02.25

represents a loss of nitrogen from the pyridazine portion of the molecule. Upon satisfactory verification of the exact composition of this fragment ion, the loss of nitrogen could conceivably be used as a diagnostic fragmentation pathway for the benzoxathiinopyridazine system.

Final discrimination between **5** and **7** requires the assignment of the ^{13}C-nmr spectrum of the molecule, the ^{1}H-nmr spectrum providing no unequivocal means of discrimination. Correct assignment of the ^{13}C-nmr spectrum of the isolated product, shown in Figure 1, requires consideration of the additivity effects for appropriate annular aza-disubstitution. In addition, the additivity effects for the methoxyl substitution must also be included in the computation. In the case of **5**, calculated ^{13}C-nmr chemical shifts may be obtained by applying aza-substitution additivities to the observed ^{13}C-nmr chemical shifts of 3-azaphenoxathiin (29) in the manner recently described for the calculated chemical shifts of 2-azaphenoxathiin (30). Based on this treatment, calculated ^{13}C-nmr chemical shifts for the as yet unknown parent 3,4-diazaphenoxathiin ring system are shown in Figure 2. It should also be pointed out that this calculation does not take into account any possible changes in the nature of the additivity values as a result of the interaction between the two nitrogen atoms (31). Calculation of the ^{13}C-nmr chemical shifts of **7** relies on the incrementation of the known ^{13}C-nmr chemical shifts of 1-azaphenoxathiin (32,33) in a similar fashion as above, which leads to the set of calculated ^{13}C-nmr chemical shifts for the unknown 1,2-diazaphenoxathiin ring system, also shown in Figure 2.

Although the calculations of the ^{13}C-nmr chemical shifts for the two possible isomeric parent ring systems are reasonably straightforward, additivities for the methoxyl group are somewhat more difficult to predict. This situation arises as a result of the relative dearth of ^{13}C-nmr chemical shift data on substituted pyridazines and the consequent unavailability of additivity constants. As an approximation, however, we have utilized the additivities reported by Sojka and co-workers (34) for the 4-methoxy substitution of pyridine. On this basis, we have obtained the calculated ^{13}C-nmr chemical shifts for **5** and **7** shown in Table I.

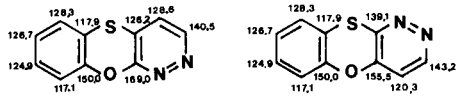
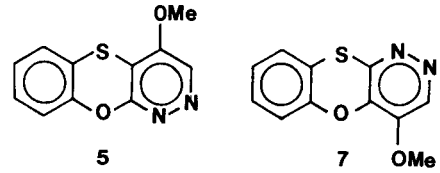


Figure 2. Calculated ^{13}C-nmr chemical shifts for the parent 3,4-diazaphenoxathiin ring system (left) and the parent 1,2-diazaphenoxathiin ring system (right).

Comparison of the anticipated chemical shifts for the pyridazine derived portion of the molecule shows some substantial differences which are crucial to the successful

Table I

Calculated ^{13}C-nmr Chemical Shifts for 1-Methoxy-3,4-diazaphenoxathiin (**5**) amd 4-Methoxy-1,2-diazaphenoxathiin (**7**) and the Asssigned ^{13}C-NMR Chemical Shifts of **5** in Hexadeuteriodimethyl Sulfoxide at 25.2 MHz.



Carbon	δ ^{13}C calculated 5	7	δ ^{13}C observed 5	Δδ
α	111.6	139.6	112.25	+ 0.7
β	169.5	140.9	165.18	− 4.3
α′	117.9	119.0	116.45	− 1.5
β′	150.0	150.0	148.79	− 1.2
1	156.4	----	158.44	+ 2.0
2	125.9	----	138.44	+12.5
3	----	128.6	----	----
4	----	148.4	----	----
6	117.1	117.1	117.82	+ 0.7
7	124.9	124.9	125.83	+ 0.9
8	126.7	126.7	127.28	+ 0.6
9	128.3	128.3	128.64	+ 0.3
-OCH_3			50.13	

Table II

^{1}H-^{13}C Spin-Coupling Constants of 1-Methoxy-3,4-diazaphenoxathiin (**5**) in Hexadeuteriodimethylsulfoxide at 25.2 MHz

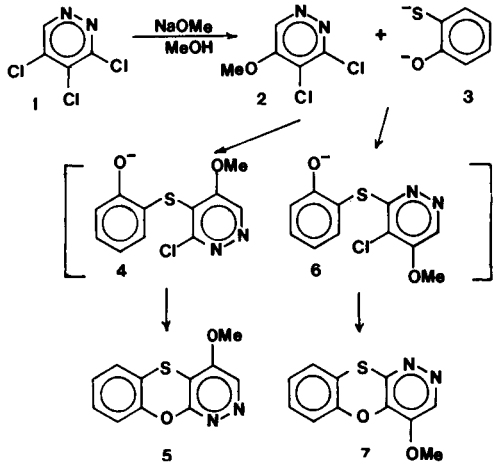
Carbon	^{1}H-^{13}C Coupling Constant (Hz) $^{1}J_{CH}$	$^{2}J_{CH}$	$^{3}J_{CH}$	$^{4}J_{CH}$
Cα	---	---	$^{3}J_{C\alpha H_2}$ = 2.5	---
Cβ	---	---	---	$^{4}J_{C\beta H_2}$ = 2.5
Cα′	---	---	$^{3}J_{C\alpha' H_6}$ = 7.4 (a) $^{3}J_{C\alpha' H_8}$ = 5.5 (a)	---
Cβ′				
C_1	---	---	---	---
C_2	$^{1}J_{C_2H_2}$ = 188.6	---	---	---
C_6	$^{1}J_{C_6H_6}$ = 163.9	---	$^{3}J_{C_6H_8}$ = 6.9	---
C_7	$^{1}J_{C_7H_7}$ = 164.7	---	$^{3}J_{C_7H_9}$ = 7.4	---
C_8	$^{1}J_{C_8H_8}$ = 164.7	---	$^{3}J_{C_8H_6}$ = 7.3	---
C_9	$^{1}J_{C_9H_9}$ = 164.9	---	$^{3}J_{C_9H_7}$ = 7.5	---

(a) May be permuted.

discrimination of the two possible isomeric products of this reaction. Most useful among these were the chemical shift for Cβ, anticipated to be δ = 169.5 ppm for **5** and 140.9 ppm for **7**; the methoxyl bearing carbon, C1, was expected to resonate at δ = 156.4 ppm for **5**, while the corresponding C4 resonance of **7** was expected to resonate at δ = 148.4 ppm. In addition, a third useful difference between these isomeric products was the position of the resonance for Cα which was anticipated to occur at δ = 111.6 in **5**, a result of both the position of the annular aza-

disubstitution and the additivity effects for the methoxyl group. In contrast, Cα in **7** was expected to resonate at δ = 139.6 ppm, the chemical shift controlled almost exclusively in this case by the 1-aza substituent; the 2-aza substituent and the 4-methoxyl group provide only minor contributions to the control of this carbon's chemical shift. Finally, an interesting and very important implication of the chemical shift of the Cα carbon is seen in the interrelation of the Cα ^{13}C-nmr chemical shift and the dihedral angle of the molecule (3), which in the case of **5** and **7**, should lead to profoundly different overall molecular shapes.

SCHEME I



Based on the discriminatory features outlined above, examination of the decoupled spectrum of the isolated product, shown in Figure 1, readily leads to the assignment of **5** as the structure of the isolated product. Good agreement was observed between the calculated and observed chemical shift data shown in Table I for all resonances of **5** with the sole exception of C2. Although C2 was predicted to resonate at δ = 125.9 ppm, it was observed to resonate at δ = 138.44 ppm. This assignment was confirmed by the primary coupling constant $^{1}J_{C_2H_2}$ = 188.6 Hz, obtained from the gated decoupled spectrum (35) of **5**. The only other ^{1}H-^{13}C spin coupling which was particularly remarkable was the three bond coupling of H2 to the Cα carbon. This coupling, $^{3}J_{C\alpha H_2}$ = 2.5 Hz, is abnormally small for a three bond coupling, since these couplings normally range from approximately 6-12 Hz. The magnitude of this coupling is, however, similar to that observed between H4′ and C2′ ($^{3}J_{C_3'H_4'}$ = 3.66), for 2-(3′-pyridyloxy)-3-nitropyridine (5). Further, it is of interest that both rings have attached to them an ether function on the intervening carbon, C3, and it is thus probable that the oxygen plays some role in the modulation of the observed coupling. The remaining ^{1}H-^{13}C couplings are summarized in Table II and were unremarkable.

In conclusion, the reaction of 5-methoxy-3,4-dichloropyridazine (**2**) with the disodium salt of *o*-mercaptophenol (**3**) leads to the formation of 1-methoxy-3,4-diazaphenoxathiin (**5**) as the sole product of the reaction. The structure of the isolated product, based on the relative reactivities of the thiophenolate and phenolate anions (28), would require either the initial attack of the thiophenolate anion on the 4-position of the pyridazine system or an unprecedented Smiles rearrangement following the attack of the thiophenolate anion at the 3-position. The mechanism of the reaction is of considerable interest since, in the former case, it would appear (26) that the 3-position should be the favored site of nucleophilic attack in **2** while for the latter case, previous work in these laboratories has shown these reactions to proceed without undergoing rearrangement. Further studies into this and related reactions are at present underway in these laboratories and will be forthcoming.

EXPERIMENTAL

All solvents utilized were reagent grade or better and were used without further purification. The *o*-mercaptophenol was obtained from Parish Chemical Company, Provo, Utah. Melting points were obtained in open capillary tubes in a Thomas-Hoover melting point apparatus and are reported uncorrected. Infrared spectra were recorded on a Perkin-Elmer Model 283 spectrophotometer as potassium bromide pellets. ^{13}C-nmr spectra were obtained on a Varian XL-500-15 spectrometer operating in the Fourier transform mode at 25.158 MHz and equipped with a Nicolet Technology TT-100 data system, an NT-400 frequency synthesizer and a TT-760 decoupler. The decoupler was set at a power of 20 watts, with irradiation centered at 7.0 ppm (δ) in the proton spectral window. The instrument was further modified for the execution of the selective excitation sequence of Freeman and co-workers (36,37) as previously described (33). Instrumental operating parameters were: pulse width, 8 μs; interpulse delay, 2 seconds; sweep width 5KHz; acquisition time, 0.8192s (4K); data size 4K (decoupled) 8K (coupled).

Synthesis of 5-Methoxy-3,4-dichloropyridazine (**2**).

The synthesis of 5-methoxy-3,4-dichloropyridazine (**2**) was carried out according to the general procedure of Itai and Kamiya (26), with the exception that sodium hydride (99% dry powder) was employed in place of the sodium metal to generate the sodium methoxide required for the reaction; ^{13}C-nmr (DMSO-d_6): δ C5, 155.00; C3, 153.59; C6, 139.85; C4, 121.80; -OCH_3, 58.35.

Synthesis of 1-Methoxy-3,4-diazaphennoxathiins (**5**).

The synthesis of **5** was begun with the preliminary preparation of the disodium salt of *o*-mercaptophenol. Thus, to 0.30 g (0.0125 mole) of 99% sodium hydride suspended in 25 ml of dry, distilled *N,N*-dimethylforanide (DMF) was added 0.75 g (0.006 mole) of *o*-mercaptophenol in an additional 10 ml of DMF. The reaction was stirred under an inert nitrogen atmosphere for three hours, after which 1.05 g (0.006 mole) of 5-methoxy-3,4-dichloropyridazine in 60 ml of DMF was slowly added. The reaction mixture darkened on addition, was stirred at room temperature for one hour and then brought to reflux for nine hours. Upon completion of the reflux, the reaction mixture was allowed to cool to room temperature and was then poured into 150 ml of ice-cold distilled water. The resultant aqueous suspension was extracted with 8 × 300 ml portions of ethyl acetate, the combined extracts were back extracted with 5 × 250 ml of distilled water, and then dried over anhydrous magnesium sulfate. The solvent was then removed *in vacuo* to give 1.06 g of semicrystalline crude yellow material. Final purification of **5** was accomplished by gradient elution chromatography using a solvent

system which was linearly varied from pure chloroform to chloroform:ethanol (96:4). The isolated crystalline material, 0.263 g (0.001 mole) 18% yield, was recrystallized from chloroform-ethanol to give a mp 223.5-225°; ms: m/z (% relatie intensity) 232 (100), 233 (13.1), 234 (5.2), 235 (9.6), 218 (4.2), 204 (8.9), 189 (3.2), 164 (3.7), 163 (19.8), 162 (10.7), 137 (5.7), 136 (31.6), 135 (3.2), 134 (5.4), 133 (2.3), 121 (2.6), 120 (2.7), 116 (4.0), 108 (11.6); ir: 1585, 1570, 1535, 1480, 1470, 1435, 1365, 1300, 1280, 1225, 1200, 1080, 1060, 1015, 860, 840, 750, 680 cm^{-1}; ^{13}C-nmr calculated *vs.* observed chemical shifts are summarized in Table I, ^{1}H-^{13}C spin-coupling constants are given in Table II.

Anal. Calcd. for $C_{11}H_8N_2O_2S$: C, 56.88; H, 3.47; N, 12.07. Found: C, 56.36; H, 4.56; N, 10.47 which corresponds to **5** co-crystallized with 1 molecule of ethanol. (Analysis calculated for complex $C_{13}H_{14}N_2O_3S$: C, 56.11; H, 5.03; N, 10.07).

Acknowledgements.

The authors would like to acknowledge the assistance of the Merck, Sharp and Dohme University Grants Program for the partial support of this work, and the National Science Foundation for Grant No. CHE-7506162 which provided funds for the acquisition of the XL-100 spectrometer system utilized in this research. The authors would also like to express their thanks to Diane Lawrence for her assistance in the preparation of this manuscript.

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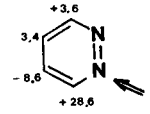
(31) An alternative calculation could be performed to generate new additivities derived from the chemical shift differentials between pyridine and pyridazine as shown below. While this set of additivity constants presumably would take into account the interaction between the two nitrogen atoms, it remains to be determined if this approach will provide a more accurate computational approach than the method successfully employed in this work.



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